

HelmholtzZentrum münchen

Deutsches Forschungszentrum für Gesundheit und Umwelt

EPA – Rochester - HMGU Ceremony and 6th Workshop 2009

05 October 2009 – 07 October 2009



Helmholtz Zentrum München

Organizing Team

A. Peters

K. Rehmann

W. Kreyling

Environmental Protection Agency

Organizing Team

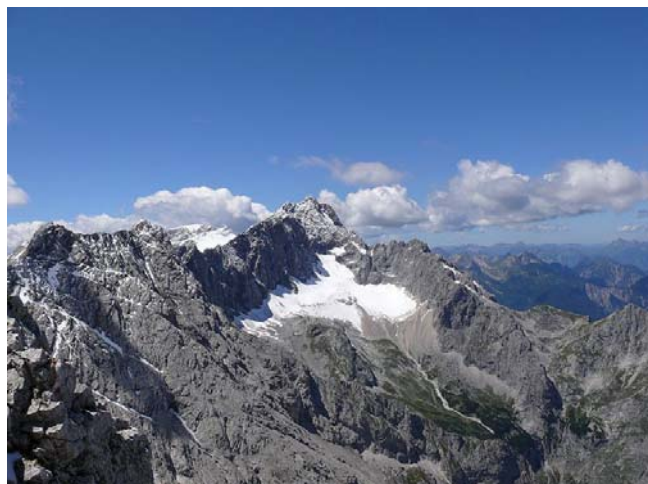
R. Devlin

D. Diaz-Sanchez

H. Koren, Durham NC

G. Oberdörster, Univ. of Rochester

Celebrating a Decade of International Collaboration on Environmental Health 1999 – 2009



Location of ceremony

05 October 2009

Helmholtz Zentrum München

- AUDITORIUM –

Ingolstädter Landstrasse 1

D-85764 Neuherberg

www.helmholtz-muenchen.de

Location of the workshop

06 – 07 October 2009

Hotel am Badersee

Am Badersee 1-5

D-82491 Grainau / Zugspitzdorf

Tel. +49 (0) 8821 8210;

www.hotelambadersee.de

HelmholtzZentrum münchen

Deutsches Forschungszentrum für Gesundheit und Umwelt

EPA – Rochester - HMGU 6th Workshop 2009



Participants

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**EPA – Rochester - HMGU
Ceremony and 6th Workshop 2009**

Program draft

**Monday,
05 October
Auditorium**

**Ceremony
Celebrating a Decade of International
Collaboration on Environmental Health
1999-2009**

15:00

Introduction

Prof. Dr. Günther Wess, Wissenschaftlich-
Technischer Geschäftsführer, Helmholtz Zentrum
München

15:20

Greetings

Prof. Dr. David Diaz-Sanchez, EPA

15:45

Ceremonial Lecture

Prof. Dr. Dr. H.-Erich Wichmann, EPI, Helmholtz
Zentrum München
Prof. Dr. Hillel Koren, EPA

16:15

**Cooperation EPA – Helmholtz Zentrum
München – a highlight example:**

Panel studies with diabetes patients

PD Dr. Annette Peters, EPI, Helmholtz Zentrum
München

Prof. Dr. Robert Devlin, EPA

17:00

Get-Together

18:30

Bus transfer to Hotel am Badersee

20:30

Informal get together

Tuesday, 06 October

Workshop in Grainau

Breakfast

09:00

Working session

I Near road studies

Chair: H.-E. Wichmann (HMGU), A. Vette (EPA)

This session will focus on planning upcoming near road studies by EPA and HMGU in an effort to leverage them against each other.

Kick off presentations (5 min): L. Neas (EPA), J. Heinrich (HMGU), M. Frampton (Rochester)

10:30

Coffee break

Additional time for adjusting and sketching common project proposals

11:30

Working session

II Exposure to ambient and traffic related particles

Chair: L. Neas (EPA), J. Heinrich (HMGU)

This session will include:

a) measuring PM and other pollutants in a near road environment

b) use of modelling to predict personal exposure to PM

c) use of exposure analysis to link sources to health effects

Kick off presentations (5 min): A. Vette (EPA), J. Cyrus / R. Zimmermann (HMGU); P. Hopke (Rochester)

13:00

Lunch break

Additional time for adjusting and sketching common project proposals

15:00

Working session

III Gene-Environment-Interactions

Chair : D. Diaz-Sanchez (EPA), A. Peters (HMGU)

This session will include :

a) Analysis of genetic factors that are associated with increased responsiveness of humans to pollutants

b) Analysis of epigenetic factors that are associated with increased responsiveness of humans to pollutants

Kick off presentation (5 min): M. Jardim (EPA), A. Schneider (HMGU), M. Frampton (Rochester)

16:30

Coffee break

Additional time for adjusting and sketching common project proposals

17:30	Working session IV Mechanisms and Responses to PM and Nanoparticles Chair: W. Kreyling (HMGU), J. Samet (EPA) <i>This session will include:</i> a) the use of imaging techniques to measure real time responses of cultured cells to various particles, including nanoparticles b) mechanisms of adjuvant effects of pollutants c) ultrafine/nanoparticle translocation, CNS effects Kick off presentations (5 min): D. Diaz-Sanchez (EPA), L. Ziegler/Heitbrock (HMGU), A. Elder (Rochester)
19:00	Dinner
21:00	Informal get together

**Wednesday, 07 October
Grainau**

	Breakfast
08:00	Working session V Future Perspectives Chairs: I. Gilmour (EPA), M. Göttlicher (HMGU) Themes: HMGU: Lung Biology, Helmholtz Cohort, Metabolomics, Systems Biology EPA: Toxicity testing in the 21 st Century Presentations (about 15 min each): R. Ramabhadran, EPA (Toxicity testing/systems biology); O. Eickelberg, HMGU Lung Biology; H.-E. Wichmann, HMGU Helmholtz Cohort; T. Illig, HMGU Metabolomics G. Oberdörster, Rochester: Predictive toxicity testing of particles
09:30	Working session including coffee Proposal writing (Finalization of Drafts)
11:00 – 12:00	Summing up Synopsis of project proposals and summary Chairs : I. Gilmour (EPA), H.-E. Wichmann (HMGU) Summaries: D. Diaz-Sanchez (EPA), A. Peters (HMGU)
12:00	Lunch break
13:00	End of workshop
13:30	Trip to Zugspitze

HelmholtzZentrum münchen

Deutsches Forschungszentrum für Gesundheit und Umwelt

EPA-Rochester-HMGU-Workshop 2009 Trip to Zugspitze

Date: October 7, 2009

Ticket: 47,00 €

Up: [Zahnradbahn](#) Grainau -> Eibsee

Bayerische Zugspitzbahn Zahnradbahn // Garmisch - Grainau - Eibsee - Zugspitzplatt												
Grainau	a 08:00	08:30	09:30	10:30	11:30	12:30	13:30	14:30	15:30	16:30	17:30	18:30
Eibsee	orb 08:15	08:45	09:45	10:45	11:45	12:45	13:45	14:45	o/c 15:45			

and then [Eibsee-Seilbahn](#) Eibsee -> Zugspitzgipfel

Eibsee-Seilbahn
vom Eibsee zum Zugsitzgipfel

Betriebszeit: von 8:00 bis 16:45 Uhr
verkehrt mind. halbstündlich // Fahrzeit 10 min. // Zwischenfahrten nach Bedarf



Down: [Eibsee-Seilbahn](#) Zugspitzgipfel -> Eibsee

Eibsee-Seilbahn
vom Eibsee zum Zugsitzgipfel

Betriebszeit: von 8:00 bis 16:45 Uhr
verkehrt mind. halbstündlich // Fahrzeit 10 min. // Zwischenfahrten nach Bedarf

and then [Zahnradbahn](#) Eibsee -> Grainau or further to Garmisch

Bayerische Zugspitzbahn Zahnradbahn // Zugspitzplatt - Eibsee - Grainau - Garmisch												
Eibsee					10:15	11:15	12:15	13:15	14:15	15:15	16:15	17:15
Grainau	07:15	a 07:58	08:30	09:30	10:30	11:30	12:30	13:30	14:30	15:30	16:30	17:30
Hammersbach	x 07:17	a 08:00	08:33	09:33	10:33	11:33	12:33	13:33	14:33	15:33	16:33	17:33
Kreuzeck-/Alpspitzbahn	x 07:20	a 08:03	08:37	09:37	10:37	11:37	12:37	13:37	14:37	15:37	16:37	17:37
Hausberg	x 07:27	a 08:10	08:46	09:46	10:46	11:46	12:46	13:46	14:46	15:46	16:46	17:46
Garmisch	o 07:30	a 08:13	08:50	09:50	10:50	11:50	12:50	13:50	14:50	15:50	16:50	17:50

To get back to Munich:

[Zahnradbahn](#) Grainau -> Garmisch

Bayerische Zugspitzbahn Zahnradbahn // Zugspitzplatt - Eibsee - Grainau - Garmisch													
Grainau		07:15	a 07:58	08:30	09:30	10:30	11:30	12:30	13:30	14:30	15:30	16:30	17:30
Hammersbach	x	07:17	a 08:00	08:33	09:33	10:33	11:33	12:33	13:33	14:33	15:33	16:33	17:33
Kreuzeck-/Alpispitzbahn	x	07:20	a 08:03	08:37	09:37	10:37	11:37	12:37	13:37	14:37	15:37	16:37	17:37
Hausberg	x	07:27	a 08:10	08:46	09:46	10:46	11:46	12:46	13:46	14:46	15:46	16:46	17:46
Garmisch	o	07:30	a 08:13	08:50	09:50	10:50	11:50	12:50	13:50	14:50	15:50	16:50	17:50

and then [D-Bahn](#) Garmisch -> Munich



Bahnhof/Haltestelle	Datum	Zeit	Dauer	Umst.	Produkte	Normalpreis
Garmisch-Partenkirchen	Mi, 07.10.09	ab 13:08	1:19	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 14:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 14:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 15:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 15:04	1:26	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 16:30				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 16:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 17:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 17:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 18:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 18:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 19:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 19:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 20:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 20:04	1:23	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 21:27				
Garmisch-Partenkirchen	Mi, 07.10.09	ab 21:04	1:22	0	RB	17,60 EUR
München Hbf Gl.27-36	Mi, 07.10.09	an 22:26				

1 Erwachsener, 2. Klasse

Proposal for Working session

I Near road studies / II Exposure to ambient and traffic related articles

APPLICATION OF ASSESSMENTS OF NEAR-ROADWAY EXPOSURES TO EXISTING BIRTH COHORTS.

Principal Investigators:

EPA: Lucas Neas, Danelle Lobdell

HMGU: Joachim Heinrich, Elaina MacIntyre

Background:

Joachim Heinrich is an international respected leader in the application of indicators of the near-roadway environment to both the GINI and LISA birth cohorts for the assessment of the impact of these exposures on childhood development, particularly the development of allergy and asthma. The U.S. National Children's Study (NCS) is a new birth cohort in 107 U.S. counties conducted by multiple research centers under the direction of EPA/CDC/NIH. In addition several near-roadway studies in European birth cohorts (PIAMA, BAMSE, LISA) will be compared with similar birth cohort studies in Canada. Experiences from these comparative studies (Elaina MacIntyre) could be used for improved strategies for the NCS.

Objectives:

To apply near-roadway assessments to the U.S. National Children's Study (NCS).

Approach/Project Plan:

EPA would coordinate a working group to develop an ancillary research proposal for NCS, including Brian Leaderer (Yale) and other U.S. researchers. Joachim Heinrich and Elaina MacIntyre would be invited to collaborate with this working group.

Anticipated Products:

An ancillary research proposal to incorporate metrics of the near-roadway environment into NCS.

Travel:

Pending approval, EPA could offer invitational travel for Joachim Heinrich and Elaina MacIntyre to attend one or more weeks.

Expected completion date:

Fall, 2011

COMPARISON OF METHODS FOR LAND-USE REGRESSION MODELING OF NEAR-ROADWAY EXPOSURES.

Principal Investigators:

EPA: Lucas Neas, Shaibal Mukerjee, Travis Smith

HMGU: Joachim Heinrich, Matthias Birk, Elaina MacIntyre

Background:

Both research groups have developed considerable expertise in the development of land-use regression models for the near-roadway environment.

Objectives:

To compare methods for the generation of proximity and volume data from geographic information systems, for the passive and active monitoring of indicator pollutants, and for the development of land-use regression (LUR) models. Specific attention should be paid on country-specific characteristics such as the composition of the fleet in terms of proportion of diesel cars and its contribution to the LUR-models.

Approach/Project Plan:

EPA has recently hired Dr. Travis Smith, a Data Management Technician with GIS experience, to assist with the development of future LUR models. After additional training and experience with the LUR models developed for El Paso and Detroit, Travis would travel to Munich for training in the approaches used by HMGU for their LUR models. A reciprocal visit by a HMGU investigator (Matthias Birk or Elaina MacIntyre) would be important. Matthias Birk is a trained geographer with specific knowledge in GIS and Arc Info programming. He joined HMGU as a doctoral student recently.

Anticipated Products:

A review paper for Environmental Health Perspectives focused exclusively on an inter-comparison of methods.

Travel:

Dr. Travis Smith would go to HMGU for an extended, multi-week stay and reciprocal Matthias Birk or Elaina McIntyre.

Expected completion date:

Fall, 2011

will be highlighted in plenary

ENVIRONMENTAL HEALTH EFFECTS IN THE DEPS PANEL STUDY FROM CHAPEL HILL AND IN THE ROCHESTER PARTICLE CENTER STUDY: A RESEARCH FOCUS ON INDIVIDUALS WITH DIABETES AND IMPAIRED GLUCOSE TOLERANCE

Principal Investigators:

EPA: Bob Devlin, Lucas Neas

HMGU: Alexandra Schneider, Annette Peters

Rochester: Günther Oberdörster, Mark Frampton

Background:

Exposure to airborne particles has been shown to be responsible for cardiovascular and hematological effects, especially in older people with cardiovascular disease. Some epidemiological studies suggest that subjects with diabetes may be a particularly susceptible population. As the number of diabetic patients is very likely to strongly increase over the next years, the search for opportunities - such as a reduction in particulate exposure - to promote better health for them is therefore a major public health task.

A joint analysis of the DEPS study by Bob Devlin and Alexandra Schneider has shown an immediate association between PM_{2.5} and endothelial dysfunction as well as a delayed association (lag of two days) between PM_{2.5} and interleukin-6 and tumor-necrosis-factor-alpha. Slight immediate changes in repolarization were also found.

Field work of the Rochester Particle Center Study has been completed and personal as well as ambient air pollution data, data on conducted ECGs and endothelial function measurements are ready for analysis. Blood markers soluble CD40Ligand, fibrinogen and C-reactive protein, interleukin-6, myeloperoxidase and plasminogen activator inhibitor-1 have already been analyzed by Rick Phipps (Rochester), Wolfgang Koenig (Ulm) and Bob Devlin (Chapel Hill), respectively.

Objectives:

The DEPS study examines effects on endothelial function, inflammation and coagulation blood markers as well as cardiac effects of short-term exposures to ambient PM_{2.5} in a panel of 22 adults with diabetes (4 repeats per participant) in Chapel Hill, NC, from Nov 2004 through Dec 2005.

The Rochester Particle Center Study objective is to examine the effect of fine and ultrafine particles (ambient as well as personal measurements) on systemic responses (acute phase reaction and pro-thrombotic states), endothelial and cardiac function (autonomic function and repolarization) as key elements of coronary vulnerability. The study was conducted in Augsburg, Germany, between March 2007 and December 2008 in subjects with type 2 diabetes mellitus, impaired glucose tolerance and potential genetic susceptibility.

Approach/Project Plan:

A further step in the DEPS study will be the analysis of PM_{2.5} components (Ron Willimas, Phil Hopke) and sources (Rachelle Duval) in association with the above mentioned health endpoints. Moreover, a publication on flow cytometry results in association with fine particles will be written together with David Diaz-Sanchez and Neil Alexis from UNC. In addition, personal measurements of PM_{2.5} (Ron

Williams) as well as modeled personal exposure to PM_{2.5} (model developed by Michael Breen) will be used together with diary information to compare the health effects of both approaches. In the same study framework there will be a publication on PM-independent temperature effects on endothelial dysfunction. In the Rochester Particle Center Study the analysis of the above mentioned health outcomes in association with air pollution measures from the Augsburg monitoring station as well with personal ultrafine particle measurements have been started and will be conducted as joint work between HMGU, EPA and Rochester. The additional personal measurements of air temperature, relative humidity and noise will be taken into account. Moreover there will be genome wide analysis data available for the whole study population. Health effects in the three different panels will be compared.

Anticipated Products:

DEPS:

- Paper on PM_{2.5} and flow cytometry
- Paper on PM_{2.5} components and health effects
- Paper on PM_{2.5} sources and health effects
- Paper on health effect of personal PM_{2.5} (measured and modeled)
- Paper on air temperature effects on endothelial function
- Paper on personal PM_{2.5} and diary information (Ron Williams)
- Paper on modeled personal PM_{2.5} exposure (Michael Breen)

Rochester Particle Center Study:

- Paper on air pollution effects on cardiac function
- Paper on air pollution effects on endothelial function
- Paper on air pollution effects on acute phase reaction and pro-thrombotic states
- Comparison of personal and ambient particle number counts including diary information (Josef Cyrus)
- Paper on gene-environment interaction

Travel:

Alexandra Schneider will visit Chapel Hill in December 2009 again and a further visit is anticipated before (or after) the ATS conference in May 2010.

Expected completion date:

DEPS: Spring 2011

Rochester Particle Center Study: 2012

Proposal for Working session

I Near road studies /

IV Mechanisms and Response to PM and Nanoparticles

ASSOCIATION BETWEEN REAL TIME MEASUREMENT OF PARTICLE MASS AND NUMBER WITH CHANGES IN HRV AND REPOLARIZATION

Principal Investigators:

EPA: Bob Devlin

HMGU: Regina Ruckerl, Alexandra Schneider, Annette Peters

Background:

Heart rate variability (HRV) has been associated with cardiovascular disease. Epidemiological studies show associations between ambient air pollution and changes in HRV. Real time personal measurements of air pollutants in this context are rare. HMGU scientists analyzed HRV data of ten volunteers measured over 24 hours in Augsburg, Germany. Subjects were fitted with a HOLTER 7-lead-ECG and portable devices measuring their exposure to particulate matter <2.5 μ m (PM_{2.5}), carbon monoxide (CO) and meteorology. Five of them additionally measured particle number concentrations (PNC). Mixed models were used to analyze the association between heart rate, high and low frequency power (HF and LF), standard deviation of all normal-to-normal (NN) intervals (SDNN), the root mean square of successive NN interval differences (RMSSD) and air pollution. A confounder model was built for each outcome separately adjusting for autocorrelation. 5-minute-ECG-data averages were analyzed in association with 5-minute-pollution-lags preceding ECG (lag0: average of 0-4 minutes up to lag11: 55-59 minutes). The unique feature of this study is the continuous personal air pollution measurement directly related to HRV parameters on a 5-minute-basis. The results show a decrease in parasympathetic activity in association with particles. The immediate reaction may indicate mediation by the autonomic nervous system in response to direct reflexes from lung receptors.

Objectives and Approach/Project Plan:

In many controlled exposure studies that take place at the EPA, subjects sit at rest while being exposed to concentrated ultrafine, fine, or coarse ambient particles. The concentration inside the chamber varies from day to day depending on the outdoor concentration that day, but it remains relatively stable during the two hour exposure. Continuous measurements of particle mass and number are taken during the exposures. Subjects are also wearing Holter monitors during the exposures. We propose to take 5 minute averages of particle mass and number during the two hour exposure period and compare them with various indices of HRV and repolarization averaged over 5 minute intervals from before, during and after particle exposure.

Anticipated Products:

Manuscript in peer-reviewed journal

Travel:

Not clear at this time

Expected completion date:

Temporal-Spatial Variation of Particles: Method Development for Epidemiological Studies – Case-Study Augsburg

Principle Investigator:

EPA/NHEERL: Lucas Neas, Brad Schultz, Lisa Baxter

HMGU: Stephanie von Klot, Josef Cyrus, Susanne Breitner

Background:

Epidemiological studies have been either addressing short-term or long-term health effects of ambient particles based on urban background stations. Recent research has indicated that exposures from major roads poses an excess health risk and is neglected in most published epidemiological studies.

The HMGU measurement station in Augsburg provides detailed characterisation of particulate matter on an hourly basis. In addition, spatial measurements are being done to better characterise the temporal-spatial variation of particles in Augsburg and to supplement data on traffic density from administrative databases.

Objectives:

The proposed project has the following objectives:

- to determine the temporal-spatial variation of fine and ultrafine particles in Augsburg,
- to determine the impact of traffic in particular;
- and to develop a conceptual framework for simultaneously assessing effects of short-term and long-term exposure.

Approach/Project plan:

- Temporal-spatial variation of particles: The measurement station is placed at an urban background site with some traffic influence. Additional spatial measurements of traffic-related pollutants are being conducted.
- Impact of traffic to the temporal-spatial variation: The analyses of measurements described above will incorporate information of traffic density for the estimation of the impact of traffic as a source on the temporal-spatial pattern.
- Conceptual framework for simultaneously assessing effects of short-term and long-term exposure by setting up of a simulation study.

Products:

- Abstracts at international conferences
- At least one peer reviewed scientific paper.

PERSONAL EXPOSURE TO COARSE AND FINE PARTICULATE MATTER

Principal Investigators:

EPA: Ron Williams, Bob Devlin

HMGU: Josef Cyrus, Alexandra Schneider

Background:

The temporal and spatial variability of ambient PM_{10-2.5} (coarse) is not well defined. Even less is known about the variability of personal exposures to this same PM size fraction. While there is a modest relationship between ambient mass concentrations of fine PM (2.5 μ m) and personal exposure, early studies would indicate that a poor or even non-existent relationship between ambient and personal PM_{10-2.5} mass concentrations exist. There is a need to further understand the relationships between ambient (community-level) measures of PM and those encountered at the personal exposure setting. Data from existing EPA and HMGU panel studies will be examined for their ability to elucidate this research opportunity. Techniques and approaches to measure personal exposure levels of various PM size fractions will be examined.

Objectives:

The proposed project would involve the following objectives:

- to determine the state of the science regarding personal exposure methodologies applicable for human exposures to fine and coarse PM, and
- to summarize existing or new data findings relative to personal exposures to PM of ambient origin.

Approach/Project Plan:

- Review existing EPA and HMGU human exposure panel study data involving PM_{2.5} and PM_{10-2.5} size fractions.
- Examine current technologies being used and their potential for providing low burden and high quality data collections

Anticipated Products:

- Abstracts at international conferences
- (tentative) A draft journal article reporting the state of the science concerning the applicability of fine and coarse PM human exposure measurements as inputs in health effect studies
- Depending upon future EPA and HMGU resources (staffing and research monies), this collaboration might have the potential for developing a joint research study design that would be integrated into a future health effect study (conducted by one or both institutions)

Travel:

No travel would be needed relative to the base products. Conference calls and shared data summaries would be used to foster communication.

Expected completion date:

December 2010- review and summarize existing data sets

December 2011-develop a review article concerning the data findings described above

Proposal for Working session

II Exposure to ambient and traffic related articles

Exposure Studies: Linkage of PM components/ Sources to Health effects

Principal Investigators:

EPA/NERL: Rachelle Duvall, David Olson

HMGU: Alexandra Schneider

Background:

Particulate matter (PM) has been shown to be associated with increased human mortality and morbidity. Fine PM (less than 2.5 μm) mass associations with adverse health impacts are well established, and recent research has also demonstrated associations between coarse PM (10 - 2.5 μm) mass and health effects. Numerous epidemiology and toxicology studies have shown that certain PM components/sources are associated with specific health outcomes however the underlying mechanisms are unclear.

Objectives:

The proposed objectives for this project are as follows:

- Determine PM sources using advanced receptor modeling tools (e.g. PMF, Unmix, CMB) or other techniques such as Scanning Electron Microscopy.
- Measure specific toxicology outcomes and/or epidemiological outcomes of interest.
- Develop methods to relate PM components/sources to health outcomes.

Approach/Project Plan:

Scope and scale of project plans to be determined. Data sets with both PM speciated data and measured health outcomes are ideal to relate health outcomes with specific PM components/sources.

Anticipated Products:

Presentation at scientific conference and/or publication in peer-reviewed journal.

Travel:

Expected completion date:

2010-2012

SPECIATION OF ORGANIC AERSOLS

Principal Investigators:

EPA: David Olson

HMGU: Ralf Zimmermann, Jürgen Schnelle-Kreis

Background:

Considerable research has been completed over the past two decades concluding that air pollution (especially particulate matter) is associated with adverse human health outcomes. Despite such improved understanding, the overwhelming amount of research has been limited to associations using comparatively simple environmental metrics, e.g., PM mass. Likewise, existing human and animal exposure studies have been limited, using only bulk measures like PM mass or restricting exposures to only one source type (e.g., diesel exhaust).

Objectives:

Use organic and inorganic source markers in future and on-going health studies evaluating exposure to air pollutants and health effects. Develop a comprehensive program aimed at characterizing and understanding specific chemical components of PM and air toxics associated with health outcomes, and relating these specific chemicals to major sources of PM and air toxics.

Approach/Project Plan:

Scope and scale of project plans to be determined. Research will involve chemical analysis for inorganic and organic source markers using ICP-MS, GC-MS, etc. to better identify sources contributing to adverse health outcomes.

Anticipated Products:

Travel:

Expected completion date:

2011-2012

GENETIC REGULATION OF EPIGENETICS

Principal Investigators:

EPA: Melanie Jardim, David Diaz-Sanchez

Background: Although the importance of epigenetic modifications to the genome has been established, there remains a lack of understanding of how the environment can change epigenetic marks, including DNA methylation, microRNA expression and chromatin remodeling. Epigenetic modifications can alter gene activity without changing the genome sequence itself and can be passed on from generation to generation. While progress has been made in understanding the consequence of epigenetic changes on gene expression, it is unclear how these processes are themselves regulated.

Objectives:

1. To determine if specific epigenetic changes can be associated with exposure to air pollutants and understand how these affect gene expression.
2. To identify differences in epigenetic marks associated with increased responsiveness and susceptibility to air pollutants
3. To understand how genetic variants affect environmentally induced epigenetic changes

Approach/Project Plan:

- Combination of genomics and systems biology
- *In vitro* studies will be used in parallel to support human exposure and panel studies and to understand mechanistic details of the genetic regulation of epigenetic changes.

Anticipated Products:

This is big proposal with huge impact. Potentially several meeting abstracts and scientific publications

Travel:

Expected completion date: Ongoing

Proposal for Working session
III Gene-Environment-Interaction /
IV Mechanisms and Response to PM and Nanoparticles

RETROSPECTIVE ANALYSIS OF ASSOCIATION BETWEEN AMBIENT LEVELS OF AIR POLLUTION AND HEALTH EFFECTS OF SUBJECTS ENROLLED IN EPA CONTROLLED EXPOSURE STUDIES

Principal Investigators:

EPA: Bob Devlin, Ana Rappold,
HMGU: Alexandra Schneider, Annette Peters
Rochester: Mark Frampton

Background:

Numerous panel studies have shown associations between outdoor levels of various pollutants, especially PM, and biological changes in volunteers (e.g. changes in HRV, blood and lung inflammation, clotting coagulation, endothelial cell function). These changes were identified by linking daily fluctuations in pollutant (measured at community monitors) with fluctuations in clinical end points. However, few panel studies have the power to adequately examine factors such as age, gender, seasonal effects, susceptibility factors such as diet or medications, etc. In addition, it is becoming increasingly clear that genetic polymorphisms play an important role in determining susceptibility to air pollutants. However, even a cursory analysis of polymorphisms requires a large sample size, typically larger than can be found in a single panel or controlled exposure study.

Objectives and Approach/Project Plan:

In every controlled exposure study run in the EPA Human Studies facility, each subject is exposed twice: once to filtered air, and once to pollutant. An extensive set of clinical end points is measured following each exposure. These include lung function, bronchoalveolar lavage (or induced sputum), Holter monitoring, blood cellular and soluble components, and endothelial cell function. In addition, detailed records are kept of subjects demographic information, medications, genotype, etc. For this study, we are proposing to extract data from the clinical measurements done following air exposures (or perhaps from pre-exposure values taken prior to pollutant exposures) from all chamber studies done in the past 5 years. These changes will be associated with air pollutant measurements in the days preceding the day clinical testing was done on the subject (taken from the EPA air monitoring network), making this essentially a large panel study which will continue to grow as more subjects are studied (an average of 50 -100 subjects are studied each year). Where genotyping data is available, we will also determine if specific polymorphisms are associated with added responsiveness.

Anticipated Products:

Manuscripts in peer-reviewed journals

Travel:

Not clear at this time

Expected completion date:

Ongoing for the indefinite future

**Proposal for Working session
IV Mechanisms and Response to PM and Nanoparticles**

MECHANISMS OF ADJUVANT EFFECTS OF POLLUTANTS

Principal Investigators:

EPA: D. Diaz-Sanchez, I. Gilmour, R. Devlin / **Rochester:** S. Georas
HGMU: J. Buters, F. Alessandrini, H. Behrendt, A. Schneider

Background:

Childhood asthma is predominantly an allergic disease. Atopic diseases are an important public health issue with a huge economic and societal burden. Although the adjuvant properties of diesel particles have been the best characterized, several pollutants are thought to promote allergy and asthma. Several members of the EPA/HMGU have studied these effects from different perspectives and proposed different putative pathways. Using clinical, animal and in vitro models, air pollutants such as PM and diesel have been shown to deviate the Th2 milieu in the mucosa, alter innate immune processes that interact with adaptive immunity, enhance allergen induced inflammation and promote the effectiveness of allergens either through carrier effects, activation of basophils and mast cells or disruption of the airway epithelial barrier.

Objectives:

The proposed project would aim to integrate different models and approaches used by the different groups to elucidate the underlying mechanisms by which air pollutants to understand how PM alters antigen presentation and thereby enhance the allergic response.

Approach/Project Plan:

The approach would be a coordinated project which utilizes panel studies, clinical human and animal exposures and in vitro studies. Preliminary studies indicate that PM may be able to modulate the immune system to promote antigen presentation. This observation requires confirmation and study into the mechanism involved.

Dendritic cells (DC) have been thought to be the quintessential antigen presenting cell (APC). We will follow up on suggestive results from both groups that have shown that PM can promote the differentiation of monocytes to a DC lineage and away from a macrophage lineage. Using flow cytometry this will be monitored following PM exposure in humans and animals and in panel studies of healthy and allergic/asthmatic subjects.

The priming of CD4+ effector T cells is induced by mature DC and controlled by regulatory T cells (Treg). Using a similar approach we will study the effect of PM on Tregs (CD4+CD25+Foxp3+) in multiple models and whether this can alter DC effects.

Recent studies suggest that basophils may also function as APCs and may be necessary to induce Th2 responses to allergens. PM can act directly on basophils to enhance allergic inflammation. The ability of PM to alter APC function of basophils will be studied using this multiple approach.

In all the models the role of PM-induced oxidative stress generation in altering antigen presentation will be tested.

Anticipated Products:

Co-authored articles.

Travel:

Some exchange of PIs for short

Expected completion date: 2012

Proposal for Working session IV Mechanisms and Response to PM and Nanoparticles

IMAGING OF PARTICLES AND LIVING CELLS: MOLECULAR IMAGING OF LPS AND PARTICLE EFFECTS ON LUNG MACROPHAGES AND EPITHELIAL CELLS.

Principal Investigators:

EPA: Jim Samet, David Diaz-Sanchez, Neil Alexis

HMGU: Thomas Hofer, Winfried Moeller, Loems Ziegler-Heitbrock

Background:

Human exposure to particulate matter (PM) began with the invention of the combustion engine and has dramatically increased during industrialization. PM represents a complex mixture of organic and inorganic compounds adsorbed onto a carbonaceous particulate core. The advent of nanotechnology and widespread application of nanoparticles, has added a growing respiratory burden of particles less than 100 nm in size.

Many epidemiological, animal and cellular studies have associated exposure to PM in the ambient air with adverse health effects [1 - 3]. Given that the route of exposure is inhalation, the respiratory tract is the first organ system encountered by these PM. The very small size of some PM size fractions allow for a deep pulmonary deposition, which results in the interaction of these particles with macrophages and epithelial cells. In addition to the pulmonary toxicity, the lung response to inhaled PM is likely to be a major contributor to extrapulmonary effects associated with PM inhalation.

Exposure of macrophages and epithelial cells to PM elicits the production of inflammatory mediators that include cytokines, eicosanoids, and reactive oxidant species [2, 4 - 5]. The antecedent processes that lead to these responses involve reversible posttranslational modifications of signalling proteins. Exposure to PM therefore constitutes an extracellular signal that is transduced by signalling processes into cellular responses that range from cell death to altered gene expression.

Lipopolysaccharide (LPS) is a constituent of the cell wall of gram-negative bacteria and is a potent activator of macrophages and bronchial epithelial cells acting via toll-like receptor 4. LPS will also induce cytokines, eicosanoids and reactive oxidant species and induces the recruitment of inflammatory cells, including macrophages.

Environmental particles can be loaded with LPS and this is most pronounced in PM derived from livestock operations, grain industry, and in cigarette smoke [6 - 7]. Since both, particles and LPS can induce similar responses it will be important to determine whether the combination of the two will lead to enhanced (synergy) or reduced responses. In-vitro studies have shown that the interaction of LPS and PM can lead to enhanced responses in macrophages [8] and this may contribute to the tissue damage as seen in COPD.

Because it affords unparalleled spatial and temporal resolution, live cell imaging is a powerful tool with which to study cellular and molecular responses to LPS and particle exposure in alveolar macrophages and epithelial cells. This microscopy approach involves real-time measurements of redox status and signaling events in living cells expressing genetically encoded fluorescence-based reporters (e.g., cytoplasmic or mitochondrial targeted redox sensitive GFP variants), redox sensitive and selective dyes (e.g., PG-1), and the application of Fluorescence Resonance Energy Transfer (FRET) and other advanced spectral imaging techniques.

Objectives:

Elucidate the mechanisms through which inhaled environmental particles affect pulmonary defense systems.

Approach/Project Plan:

The focus of the investigations to be conducted in this project is on the response of lung macrophages and monocytes (as their precursors), and epithelial cells to PM exposure. Both cell types express toll-like receptor 4 (TLR4) and produce a variety of pro-inflammatory factors [1, 2, 4-5, 9], or anti-microbial peptides [3]. As particles are known to alter cellular responses towards LPS challenge [8], it is of interest to investigate the interaction of LPS and ultrafine / nano particles on cellular function. The approach can be easily expanded to include co-culture experiments of macrophages and epithelial cells in order to further approximate in vivo conditions. Generation of H₂O₂ will be the main read-out both in vitro and in in-vivo after inhaled challenge with particles and LPS. Transcriptome and proteome analyses will determine the impact of the signalling events initiated by LPS and UF exposure on gene expression in these cells.

A second focus of this work is the development and application of molecular imaging approaches in the study of the adverse effects of environmental particles. Ongoing studies are evaluating fluorescent reporters of redox status, reactive oxygen species and mitochondrial function using advanced spectral confocal microscopy instrumentation available in Chapel Hill. The aim of this work is to implement methodologies that can produce mechanistic data with sufficient spatial and temporal resolution for use in computational modelling of the mode of action of environmental agents.

Anticipated Products:

Development of integrated imaging approaches to the study of the effects of environmental contaminants in human lung cells in-vitro and in-vivo. Manuscripts, presentations at national and international conferences, training of doctoral and postdoctoral students.

Travel:

One visit per year on each side of the agreement, each period to be 2-4 weeks in duration.

Expected completion date:

2012

ACCESS OF INHALED NANOPARTICLES TO THE BRAIN

Principal Investigators:

EPA: Bob Devlin, Kevin Dreher

HMGU: Wolfgang G. Kreyling, Manuela Semmler-Behnke

Univ. Rochester: Günter Oberdörster, Alison Elder

Background:

Because of the small size of nanoparticles (NP; > 100nm) there is a potential risk that NP can reach the brain tissues via two pathways:

1. neuronal pathway: Oberdörster et al. have shown the translocation of a small fraction of NP from the nasal passages into the olfactory bulb and to further brain tissues. In addition, there is a neuronal pathway from the thorax via ganglia into the brain.
2. systemic pathway: Kreyling et al. have shown that a small fraction of NP can access the brain once they have crossed the air-blood barrier in the lungs and circulate systemically.

There is evidence that certain proteins, like apolipoproteins A1 or E and transferrin, can modulate the transport of NP across the brain-blood-barrier (Kreuter et al.).

Objectives:

In this project we aim to quantitatively determine the contribution of the above mentioned pathways towards brain tissue by different inhalation protocols.

According to our hypothesis on the underlying mechanism, we aim to better understand the role of the above mentioned proteins on both pathways and how this is modulated by NP properties.

Approach/Project Plan:

1. We aim to quantify the fraction of selected NP of gold, TiO₂ and Ag which penetrates into the brain tissue. By the distinct methods of either nose-only-inhalation versus intubation-ventilation-exposure we will be able to differentiate between both NP pathways. We will challenge how NP properties like the size or surface modification will affect these pathways.
2. We also aim to determine the role of the above mentioned proteins on the effect of NP uptake by the brain. For that pre-fabricated complexes of NP and proteins will be administered to rodent models and the dynamics of uptake will be recorded as a function of NP properties.
3. In addition, we will rank the binding efficacy of the NP according to their properties and a number of proteins from blood serum and broncho-alveolar lavage fluid which had been determined to bind to NP.

Anticipated Products:

1. Better understanding of the toxicology of inhaled NP with a special emphasis on their effects on CNS.
2. Providing nanomedicinal concepts of threatment of brain diseases.

Travel:

1-2 visits of 1-2 weeks; visits shall combine stops at both US labs.

Expected completion date:

3 years after start of project.

HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO SMOKE FROM WILDFIRES

Principal Investigators:

EPA: Ana Rappold, Bob Devlin, Martha Carraway

HMGU: Alexandra Schneider, Annette Peters

Background:

A wildfire near the Pocosin Wildlife Refuge in the summer of 2008 produced PM emissions far in excess of values normally experienced in eastern North Carolina. This fire burned continuously for nearly two months. It is predicted that communities impacted by the smoke plume from the fire will have increased numbers of hospitalizations for respiratory and cardiovascular problems. This should enable the EPA to determine the potential health effects associated with inhalation of smoke from the Pocosin wildfire because, unlike wildfires in southern California, there are very few sources of PM in eastern North Carolina.

Objectives and Approach/Project Plan:

This is a secondary data analysis consisting of a retrospective observational study of association between PM_{2.5} levels and outpatient and emergency department visits, and hospital admissions for acute cardiopulmonary and thrombotic causes due to exposure to fire smoke. We will test the hypothesis that exposure to PM_{2.5} in biomass smoke is associated with increased hospital admissions for cardiopulmonary causes. This case crossover study will monitor daily PM concentrations throughout central and eastern North Carolina, and attempt to link increased hospitalization admissions for cardiopulmonary causes with days following elevated PM concentrations. Smoke plume images and wind direction back trajectories will be used in conjunction with the monitoring data to construct a model predicting daily exposure around a person's address. Hospital and emergency room visits in eastern North Carolina for cardiovascular and respiratory events will be obtained through the Durham VA network and the eastern NC affiliated hospital network.

Anticipated Products:

Manuscripts in peer-reviewed journals

Travel:

Not clear at this time

Expected completion date:

Summer of 2110